Award Number: W81XWH-13-1-0091

TITLE: **Targeting Androgen Receptor in Breast Cancer: Enzalutamide as a Novel Breast Cancer Therapeutic**

PRINCIPAL INVESTIGATOR: Dr. Anthony Elias

CONTRACTING ORGANIZATION: Regents of the University of Colorado
Aurora, CO 80045

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PREPARED FOR: U.S. Army Medical Research and Materiel Command
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Enzalutamide has clinical activity in breast cancer as a single agent and in combination with exemestane. Activity is seen in both triple negative AR+ BC and also ER+AR+ BC. Clinical data in Her2+ AR+ BC is too immature to make conclusions. The proposed clinical trials for Years 3-5 appear to be justified based on clinical activity and the current preclinical data.

**15. SUBJECT TERMS**

Breast cancer (BC) subtypes; androgen receptor (AR); preclinical modeling; enzalutamide; AR inhibition; resistance mechanisms; predictive biomarkers.

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Award Number W81XWH-13-1-0091 Annual Report (Year 2) (revised)

Title: Targeting Androgen Receptor in Breast Cancer: Enzalutamide as a Novel Breast Cancer Therapeutic

Collaborating/Partnering PI: Anthony D Elias, MD

Contracting Organization: University of Colorado Anschutz Medical Campus

Report Date: 8/15/2014-8/14/2015

Type of Report: Second Annual Progress Report

**Introduction**

The central thesis of this grant is to understand the role of AR signaling in breast cancer subtypes, and understand how to best use an inhibitor of AR signaling, enzalutamide (enza), as a therapeutic agent in breast cancer. With the recognition that AR is expressed in all subtypes of breast cancer, that overexpression is frequently associated with relative resistance to therapy (both anti-estrogen and chemotherapy) (work of our group and others), and with the advent of increasingly potent AR signaling inhibitors in prostate cancer, the area of anti-AR therapeutics in breast cancer is one of the most active worldwide. The preclinical portion of this grant serves to understand mechanism of action of AR signaling inhibition alone or in combination with other targeted agents in ER+, Her2+, or TNBC in preclinical models, and then perform biomarker analysis in human tissues obtained before, during and after treatment with enzalutamide. The clinical portion of this grant serves to obtain these tissues in concert with the overall clinical development of enzalutamide in the subtypes of breast cancer.

**Keywords**

Breast cancer (BC) subtypes; androgen receptor (AR); preclinical modeling; enzalutamide; AR inhibition; resistance mechanisms; predictive biomarkers; targeted therapy.

**Overall Project Summary**

This report will include both the tasks that were mandated in the SOW, but also will highlight the therapeutic clinical results from the companion therapeutic trials that were sponsored by our Pharma partners, Medivation and Astellas.

**Clinical Aim 1: To identify pretreatment molecular characteristics associated with lack of response and/or prolonged PFS (Patient Tissues).**

**Task 1: Serial Biopsy Trial (Elias, Traina, Schwartzberg, Petricoinadvocates, Richer)**

- The DOD sponsored serial biopsy trial titled "Exploratory Development of Predictive Biomarkers for Patients with Androgen-Receptor Positive (AR) Breast Cancer (BC) Treated with Enzalutamide (MDV3100); COMIRB 13-1473," is activated at the University of Colorado site and the West Clinic/University of Tennessee site.
- 6 patients with serial biopsies enrolled.
    - Tissues have been processed by the UCCC Tissue Bank and distributed to the laboratories of Richer and Petricoin.

- RPPA has been performed and is currently under analysis
- DNA mutational analysis has been performed.
- RNA preparations made
- IHC done for ER/AR/Ki67 and others in process.
- Please see the Annual Report for Award Number W81XWH-13-1-0090 for all laboratory work done on the tissues and for all preclinical work.

- Accrual to this trial is not yet completed due to the limited number of therapeutic trials available to the participating institutions. This biopsy trial was a companion to therapeutic trials of enzalutamide in breast cancer sponsored by Medivation and Astellas. Those therapeutic trials however were opened to large numbers of institutions that were not part of our DOD grant, and thus were completed very quickly.
- On the other hand, the clinical development of enzalutamide was enhanced, making possible the forward-thinking investigator-sponsored trials as outlined for Years 3-5 in our grant.
- New trials are being developed with enzalutamide for breast cancer which will be suitable for our serial biopsy trial.
- Due to changes in personnel (Dr. LoRusso moved to Yale Cancer Center), Karmanos Cancer Center was deactivated, and with the approval of the Dept of Defense, the University of Tennessee was activated (PI, Lee Schwartzberg, MD).

**Task 2: Accrue 12 patients treated with enzalutamide onto serial biopsy trial (Elias, LoRusso, Traina, advocates) Year 0-Year 2 Month 7**

- First 12 patients accrued completed (12) Month 7
- First 12 patients – clinical database complete Month 15
- All initial biopsies collected from 1$^{st}$ 12 patients Month 12

As above, only the first 6 patients have been accrued. Currently only one therapeutic trial is available to accrue additional patients (AR+ Her2+ ER any) treated with trastuzumab plus enzalutamide. Once the new investigator sponsored and pharma-sponsored trials are open to accrual, serial biopsies will again become possible.

**Task 3: Tissue assays and bioinformatics analysis (Richer, Thor, Jones, Elias, LoRusso, Traina, Petricoin, Gao)**

- First 12 patients completed Month 18
- Bioinformatic analysis Month 24

The first 6 patients have completed tissue acquisition, assays have been performed and bioinformatic analysis is currently in progress.

- Please see the Annual Report for Award Number W81XWH-13-1-0090 for all laboratory work done on the tissues and for all preclinical work.

**Clinical Aim 2: To determine if a decrease in Ki67 or increase in apoptosis as measured by TUNEL in biopsies taken before treatment as compared to after 2-4 weeks of treatment or other to be determined genes or proteins are associated with lack of response and/or prolonged PFS.**

**Task 1: Accrue 24 patients treated with single agent enzalutamide (Elias, LoRusso, Traina, advocates)**

- First half of patient accrual completed (12) Month 15
- First 12 patients – clinical database complete Month 15

- All 2-week biopsies collected from 1st 12 patients Month 15

**Task 2: Tissue assays and bioinformatics analysis (Richer, Thor, Jones, Elias, LoRusso, Traina, Petricoin, Gao)**

- 12 single agent patients Month 18
- Bioinformatic analysis completed Month 24

The first 6 patients have completed tissue acquisition, assays have been performed and bioinformatic analysis is currently in progress.

- Please see the Annual Report for Award Number W81XWH-13-1-0090 for all laboratory work done on the tissues and for all preclinical work.

**Clinical Aim 3: To determine if changes in molecular determinants between pre-treatment biopsies and tissue at time of disease progression can help identify resistance mechanisms.**

**Task 1: Accrue 24 patients treated with single agent enzalutamide (Elias, LoRusso, Traina, advocates)**

- All relapse biopsies collected from 1st 12 patients Month 24

Three of the six patients with relapse have been biopsied at time of relapse.

- Please see the Annual Report for Award Number W81XWH-13-1-0090 for all laboratory work done on the tissues and for all preclinical work.

**Clinical Aim 4:** To determine if enza can overcome *de novo* resistance to exemestane in postmenopausal women with T2 or larger ER+ BC treated preoperatively.

**Task 1: Trial II: Randomized Preoperative trial in AR+/ER+ BC (Elias, LoRusso, Traina, advocates, Richer)**

- Written protocol completed Month 21
- Submitted to Scientific Review Committee Month 21
- Submitted to IRBs (all institutions) Month 22
- DoD Human Research Protection Office (HRPO) Month 24

The clinical development of enzalutamide in breast cancer has been rapid. Both Medivation and Astellas have been fully committed to this endeavor. Findings are summarized:

- The phase I of single agent enzalutamide has been completed and confirmed that the FDA approved dose in prostate cancer in men (160 mg daily) is safe and tolerable in women. Additionally, the pharmacokinetic profile of enzalutamide in women is similar to that in men.
- Because enzalutamide is a very strong p450 CYP3A4 inducer, several phase Ib trials have been completed to examine the pharmacologic interaction of enza with other anti-estrogen agent (anastrozole, exemestane) in ER+ BC.
- Enzalutamide when added to anastrozole 1 mg daily reduced the AUC of anastrozole alone by 80%. This was associated with an increase in serum estradiol in some patients. For this reason, this combination is no longer in development.
- Enzalutamide when added to exemestane 25 mg daily reduced the AUC of exemestane by about 50%. This was not associated with an increase in estradiol. However, since the FDA approval for exemestane included approval for double dose exemestane (50 mg daily) when combined with strong CYP3A4 inducers, enza plus exemestane 50 mg daily was evaluated. Pharmacokinetic analysis of this

combination demonstrated that exemestane 50 mg AUC (when combined with enza) was equivalent to exemestane 25 mg daily alone. As presented at ASCO 2014. Of 39 evaluated patients, 12 remain on therapy for more than 16 weeks (range 114-450 days). Thus this combination is moving forward in development.

- A current PK trial combining enza with fulvestrant is completed and will be reported at SABCS 2015 (Elias et al).
- The initial immunohistochemistry assay for AR used a 10% staining cutoff to determine positivity. We have switched from DAKO to Ventana antibody due to more sensitive and specific assay. With the observation preclinically that cell lines that had lower levels of AR expression were sensitive to enzalutamide inhibition, the more recent clinical trials are now using a cutoff of 1% to select eligible patients.
- A randomized double-blinded phase II trial of exemestane with or without enzalutamide in women with metastatic ER+ AR+ breast cancer has completed accrual and is maturing.
- A phase Ib of single agent enza in AR+ TNBC was completed. A phase II trial has been reported at ASCO 2015.
- Based on our preclinical work, a trial of enzalutamide plus trastuzumab has opened in 3rd or greater line Her2+ AR+ BC. These patients are eligible for our ongoing DOD grant biopsy trial.
- The LOI for Clinical Aim 4 investigator initiated trial has been prepared and is ready for submission to Medivation and Astellas for their approval (and agreement to supply enzalutamide).

**Clinical Aim 5:** To determine the maximum tolerated dose and toxicity of enza when combined with the most promising combinations as defined in the preclinical modeling experiments during Years 1-2. As an example, a combination of enza with everolimus +/- a chemotherapy agent in previously treated metastatic TNBC.

**Task 1: Trial III: Phase I/II trial in AR+/TN BC: Enzalutamide plus everolimus (Traina, Elias, LoRusso, advocates, Richer)**

- Written protocol completed Month 21
- Submitted to Scientific Review Committee Month 21
- Submitted to IRBs (all institutions) Month 22
- DoD Human Research Protection Office (HRPO) Month 24

Support for this trial was not granted by Medivation and Astellas.
An alternative trial, as presented at the Milestone Meeting in May 2015, was a Phase I/II trial in AR+ ER+ BC: Enzalutamide plus exemestane or fulvestrant with the addition of either everolimus or palbociclib. This LOI was submitted to Medivation and Astellas and is currently under review.

**Key Research Accomplishments:**

Enzalutamide has clinical activity in breast cancer as a single agent and in combination with double dose exemestane.

Tissues from 6 patients have been processed, RPPA, IHC and DNA mutation analysis has been completed. Bioinformatic analysis underway.

- Please see the Annual Report for Award Number W81XWH-13-1-0090 for all laboratory work done on the tissues and for all preclinical work.

**Conclusion:**

Enzalutamide has clinical activity in breast cancer as a single agent and in combination with exemestane. Activity is seen in both triple negative AR+ BC and also ER+AR+ BC. Clinical data in Her2+ AR+ BC is too immature to make conclusions. The proposed clinical trials for Years 3-5 appear to be justified based on clinical activity and the current preclinical data.

**Publications, Abstracts, and Presentations:**

Papers:
Dawn R. Cochrane, Sebastian Bernales, Britta M. Jacobsen, Diana M. Cittelly, Erin N. Howe, Nicholas C. D'Amato, Nicole S. Spoelstra, Annie Jean, Paul Jedlicka, Kathleen C. Torkko, Andy Protter, Anthony D. Elias and J. K. Richer. Role of the Androgen Receptor in Breast Cancer and Preclinical Analysis of Enzalutamide. BREAST CANCER RESEARCH 2014 Jan 22;16(1). PMID: 24451109

Designated as Highly Cited by the journal Breast Cancer Research.

Barton VN, D'Amato NC, Gordon MA, Lind HT, Spoelstra NS, Babbs B, Heinz RE, Elias AD, Jedlicka P, Jacobsen BM, Richer JK. Multiple molecular subtypes of triple negative breast cancer depend on androgen receptor for proliferation and invasion. Molecular Cancer Therapeutics 2015; 14: 769-778. PMID: 25713333

Barton VN, Gordon MA, Christenson JL, D'Amato NC, Elias A, Richer JK. Androgen receptor biology in triple negative breast cancer: a case for AR+ and quadruple negative disease subtypes. Horm Cancer 2015 Jul 23, epub ahead of print. PMID: 26201402.

Abstracts:
D'Amato, NC, D Cochrane, N Spoelstra, A Chitrakar, B Babbs, A Protter, AD Elias, and J Richer. (Mar 2014) Inhibiting Androgen Receptor Nuclear Localization Decreases ER Activity and Tumor Growth in ER+ Breast Cancer. University of Colorado Postdoctoral Research Day, Aurora, CO. * won best overall poster award.

Barton VN, D'Amato N, Gordon M, Elias, A, and JK Richer. Targeting androgen receptor decreases proliferation and invasion in preclinical models of triple negative breast cancer. Presented at University of Colorado Cancer Center Annual Retreat "Novel Experimental Models for Cancer Research," September 2014. * Won outstanding poster award.
Elias A, Richer JK, LoRusso P, Peterson AC, Steinberg J, Mordenti J, Lopez C, Hudis C, Traina T. MDV3100-08: A phase 1 open-label, dose-escalation study evaluating the safety, tolerability, and pharmacokinetics of MDV3100 in women with incurable breast cancer. ASCO 2012, TPS668.

Traina TA, Yardley, DA, Patel M, Schwartzberg L, Elias A, Gucalp A, Peterson AC, Hannah A, Gibbons J, Khondker Z, Hudis CA, LoRusso P. A phase 1 open-label, dose-escalation study evaluating the safety, tolerability, and pharmacokinetics of enzalutamide (previously MDV3100) alone or in combination with an aromatase inhibitor in women with advanced breast cancer. SABCS 2013 PD3-6 (A938), accepted, poster discussion.

Traina TA, Yardley, DA, Patel M, Schwartzberg L, Elias A, Gucalp A, Peterson AC, Hannah A, Gibbons J, Khondker Z, Hudis CA, LoRusso P. A phase 1 open-label, dose-escalation study evaluating the safety, tolerability, and pharmacokinetics of enzalutamide (previously MDV3100) alone or in combination with an aromatase inhibitor in women with advanced breast cancer. SABCS 2013 PD3-6 (A938), accepted, poster discussion.

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Schwartzberg LS, Yardley DA, Elias A, Patel MR, Gucalp A, Burris HA, Peterson AC, Hannah AL, Blaney ME, Gibbons J, Tudor IC, Steinberg JL, LoRusso P, Infante JR, Hudis CA, Traina TA. Enzalutamide plus exemestane: a pilot study to assess safety, pharmacokinetics, and effects on circulating estrogens in women with advanced hormone-positive breast cancer. Proc ASCO 2014.

Elias AD, Burris HA, Patel MR, Schwartzberg LS, Richer JK, Kavalerchik E, Stopatschinskaja S, Gibbons J, Markova D, Steinberg JL, Traina TA. MDV3100-08: a phase I study evaluating the safety and pharmacokinetics of enzalutamide plus fulvestrant in women with advanced hormone receptor-positive breast cancer. Proc SABCS 2015, accepted poster presentation.

Website(s) or other Internet site(s)
List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Expert Opinion piece in Oncology PracticeUpdate http://www.practiceupdate.com/journalscan/9370 or http://prac.co/j/5960d32c-988b-423e-ba24-14ca5c8cc39a?elsca1=soc_share-this acknowledgement of federal support –no

Highlight of Cochrane DR et al Breast Cancer Research 2014 in Feb issue of 2014 NATURE REVIEWS CLINICAL ONCOLOGY. acknowledgement of federal support –yes

Dr. Elias gave the following presentation:
Elias A. What is the androgen receptor doing in breast cancer and can we target it? 14th Annual International Congress on the Future of Breast Cancer. PER. Huntington Beach, CA 7/17/15.

**Inventions, Patents and Licenses:** Nothing to report

**Reportable Outcomes:** Nothing to report.
Please see the Annual Report for Award Number W81XWH-13-1-0090 for all laboratory work done on the tissues and for all preclinical work.

**Other Achievements:** Completed phase I/Ib clinical trials of single agent enzalutamide and in combination with anastrozole, exemestane, and fulvestrant. Please see publication/abstract list.

**Traina TA, Yardley, DA, Patel M, Schwartzberg L, Elias A, Gucalp A, Peterson AC, Hannah A, Gibbons J, Khondker Z, Hudis CA, LoRusso P. A phase 1 open-label, dose-escalation study evaluating the safety, tolerability, and pharmacokinetics of enzalutamide (previously MDV3100) alone or in combination with an aromatase inhibitor in women with advanced breast cancer. SABCS 2013 PD3-6 (A938), accepted, poster discussion.** This demonstrated that the PK and single agent toxicity of enzalutamide in female breast cancer patients was the same as that of male prostate cancer patients.

**Traina TA, Yardley DA, Patel MR, Schwartzberg LS, Elias A, Gucalp A, Blaney ME, Gibbons J, Hudis CA, LoRusso P. A phase 1 open-label study evaluating the safety, tolerability, and pharmacokinetics of enzalutamide alone or combined with an aromatase inhibitor in women with advanced breast cancer. IMPAKT 2014 Breast Cancer Conference May 2014, Abstract 214.** This demonstrated that enzalutamide caused an 80% drop in AUC of anastrozole and a 50% drop in the AUC of exemestane via CYP3A4 induction. No new safety signals were observed.

**Schwartzberg LS, Yardley DA, Elias A, Patel MR, Gucalp A, Burris HA, Peterson AC, Hannah AL, Blaney ME, Gibbons J, Tudor IC, Steinberg JL, LoRusso P, Infante JR, Hudis CA, Traina TA. Enzalutamide plus exemestane: a pilot study to assess safety, pharmacokinetics, and effects on circulating estrogens in women with advanced hormone-positive breast cancer. Proc ASCO 2014.** This demonstrated that enzalutamide plus double dose exemestane resulted in equivalent PK and maintenance of estradiol suppression as single agent standard dose exemestane. No new safety signals were observed. Therefore for ongoing trials, double dose exemestane (eg, 50 mg daily) will be used.

**Elias AD, Burris HA, Patel MR, Schwartzberg LS, Richer JK, Kavalerchik E, Stopatschinskaja S, Gibbons J, Markova D, Steinberg JL, Traina TA. MDV3100-08: a phase I study evaluating the safety and pharmacokinetics of enzalutamide plus fulvestrant in women with advanced hormone receptor-positive breast cancer. Proc SABCS 2015, accepted poster presentation.** This demonstrated that there was no significant PK interaction between fulvestrant and enzalutamide. No new safety signals were observed.

Please see the Annual Report for Award Number W81XWH-13-1-0090 for all laboratory work done on the tissues and for all preclinical work.

**References:**

Papers:
Dawn R. Cochrane, Sebastian Bernales, Britta M. Jacobsen, Diana M. Cittelly, Erin N. Howe, Nicholas C. D'Amato, Nicole S. Spoelstra, Annie Jean, Paul Jedlicka, Kathleen C. Torkko, Andy Protter, Anthony D. Elias and J. K. Richer. Role of the Androgen Receptor in Breast Cancer and Preclinical Analysis of Enzalutamide. BREAST CANCER RESEARCH 2014 Jan 22;16(1). PMID: 24451109

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Elias AD, Burris HA, Patel MR, Schwartzberg LS, Richer JK, Kavalerchik E, Stopatschinskaja S, Gibbons J, Markova D, Steinberg JL, Traina TA. MDV3100-08: a phase I study evaluating the safety and pharmacokinetics of enzalutamide plus fulvestrant in women with advanced hormone receptor-positive breast cancer. Proc SABCS 2015, accepted poster presentation.

D'Amato NC, Jacobsen BM, Cochrane DR, Spoelstra NS, Babbs BL, Elias A, Richer JK. Inhibiting androgen receptor nuclear localization decreases estrogen receptor (ER) activity and tumor growth in ER+ breast cancer. Proc SABCS 2014, P3-04-06

Gordon MA, D'Amato N, Gu H, Wong D, Elias A, Richer JK. Targeting multiple pathways in breast cancer: Androgen receptor, HER2, and mTOR. Proc SABCS 2014, P6-03-07.

Gordon MA, D'Amato N, Gu H, Liu B, Elias A, Richer JK. The anti-androgen enzalutamide synergizes with trastuzumab and everolimus to inhibit breast cancer growth via distinct mechanisms. Endocrine Society 2015.

Website(s) or other Internet site(s)
List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Expert Opinion piece in Oncology PracticeUpdate http://www.practiceupdate.com/journalscan/9370 or http://prac.co/j/5960d32c-988b-423e-ba24-14ca5c8cc39a?elsca1=soc_share-this acknowledgement of federal support –no

Highlight of Cochrane DR et al Breast Cancer Research 2014 in Feb issue of 2014 NATURE REVIEWS CLINICAL ONCOLOGY. acknowledgement of federal support –yes